REMARKS

Entry of the instant amendment and reconsideration of the above-identified application as amended is respectfully requested.

Claims 7, 8, 11-16, 19 and 28-42 are pending in the application.

Please cancel claims 8, 15-16, 19, 28-31 and 38-42 without any prejudice of Applicants' rights to file a continuing application(s) directed to the subject matter cancelled by the instant amendment.

Accordingly, upon entry of the instant amendment, claims 7, 11-14 and 32-37 remain in the application.

In the Claims

Claim 7 has been amended to limit the methods of the present invention to those which synergistically enhance the chemotherapeutic treatment of melanoma, pancreatic carcinoma, colon carcinoma and lung carcinoma. Furthermore, claim 7 has been amended to cover only the concurrent administration of an adenosine A_3 receptor antagonist and a chemotherapeutic agent.

In addition, claim 7 has been amended to limit the adenosine A_3 receptor antagonists to MRE3008F20, MRE3046F20, MRE3055F20, MRE3062F20, IL-10 and IL-11, and the chemotherapeutic agents to paclitaxel, docetaxel, irinotecan, videsine, vinblastine and doxorubicin.

Claim 11 and claim 12, which also has been amended to depend from claim 11, have been amended to limit the methods to a synergistic enhancement of the chemotherapeutic treatment of melanoma.

Claim 13 has been amended to limit taxane family compounds to paclitaxel and docetaxel.

Claim 14 has been amended to limit vinca alkaloid compounds to vindesine.

Claim 32 has been amended to limit the methods to a synergistic enhancement of the chemotherapeutic treatment of pancreatic, colon and lung carcinomas. Moreover, claim 32 has been amended to depend from claim 7.

Claim 33 has been amended to limit adenosine A_3 receptor antagonists to MRE3008F20, IL-10 and IL-11.

Claims 34-37 have been amended to provide proper antecedent basis.

All the instant claims 7, 11-14 and 32-37, as amended herein, are supported by experimental data demonstrating synergistic enhancement of the chemotherapeutic treatment of melanoma, pancreatic carcinoma, colon carcinoma and lung carcinoma by employing the specifically disclosed combinations of the present invention.

Claim Rejection under 35 U.S.C. § 112, Second Paragraph

Claims 7, 8, 11-16, 19 and 28-42 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention, because claim 7, and claims depending thereof, recite the term "countering". In the Examiner's opinion the metes and bounds of the term "countering" are not defined by the claim, and the specification fails to describe any supportive definition for the term "countering".

Applicants disagree. It is respectfully submitted that the meaning of the term/verb "counter" is well understood, e.g., Merriam-Webster Online Dictionary defines the meaning of the term/verb "counter" as to oppose, to offset and/or to nullify. Furthermore, the specification of the instant application describes, e.g., in the first paragraph on page 13, that "The combination therapy enhances the effect of the chemotherapeutic cancer agent and <u>prevents</u> multi-drug resistance from developing". Likewise, in the second paragraph on page 13 it is stated that "Similarly, the combination therapy can be used for <u>treating</u> cancers that have already developed multi-drug resistance. In this case, the high affinity adenosine A_3 receptor antagonist counters the existing MDR while further enhancing the effect of the chemotherapeutic cancer agent". Clearly, the meaning of the term "countering" of claim 7 is distinctly defined and could be substituted, e.g., with its synonyms or the phrase "preventing and/or treating".

In view of the above, it is respectfully submitted that the rejection under 35 U.S.C. § 112, second paragraph, is not warranted and should be withdrawn.

Claim Rejection under 35 U.S.C. § 102(b)

Claims 7-8, 11-14, 16, 19, 28-29, 31-33, 35, 37-38, 40 and 42 are newly rejected under 35 U.S.C. § 102(b) as being anticipated by Leung et al. (US 6,326,390; IDS reference AD, filed January 9, 2004)

The following is a quotation from MPEP § 706.07(a):

> "Under present practice, second or any subsequent actions on the merits shall be final, except where the examiner introduces a new ground of rejection that is neither necessitated by applicant's amendment of the claims, nor based on information submitted in an information disclosure statement filed during the period set forth in 37 CFR 1.97(c) with the fee set forth in 37 CFR 1.17(p)."

It is respectfully submitted that clearly the new ground of rejection under 35 U.S.C. § 102(b) as being anticipated by Leung et al. was not necessitated by Applicants' amendment of the claims because the only claim amendment that was made in the previous communication by Applicants, filed on February 28, 2008, was the amendment of claim 7 by replacing the term "suppressing" with the term "countering".

Likewise, the new ground of rejection, i.e., Leung et al., was cited on a PTO-1449 form submitted in an Information Disclosure Statement filed on January 9, 2004 under 37 C.F.R. § 1.97(b).

Furthermore, the Examiner cites a new reference, a webpage by Alexis Biochemicals entitled "Multidrug Resistance" (12/2001), in connection with the newly applied rejection under 35 U.S.C. § 102(b).

In view of the above, it is respectfully submitted that the finality of the instant Office action is not warranted and should be withdrawn.

As to Leung et al., Applicants acknowledge that the reference discloses a method of inhibiting tumor growth by the administration of an adenosine A_3 receptor antagonist to a patient either alone or in combination with other anti-tumor agents such as chemotherapeutic agents (cytotoxic agents). However, Leung et al. does not teach or suggest that the administration of an adenosine A_3 receptor antagonist in combination with

a chemotherapeutic agent would result in a synergistic enhancement of the chemotherapeutic treatment of melanoma, pancreatic carcinoma, colon carcinoma and lung carcinoma. In other words, Leung et al. does not provide any reasonable expectation of success to achieve a synergistic effect on the chemotherapeutic treatment of melanoma, pancreatic carcinoma, colon carcinoma and lung carcinoma by employing a combination an adenosine A_3 receptor antagonist with a chemotherapeutic agent, in particular, by employing those combinations specifically disclosed and claimed in the instant application.

In fact, Leung et al. discloses, as a preferred embodiment, a combination therapy which comprises an adenosine A_3 receptor antagonist, a cytotoxic agent and an anti-angiogenesis agent (column 6, lines 23-30). Thus, one skilled in art would expect that all three agents are required to obtain a beneficial therapeutic effect. In other words, one skilled in the art would not expect that combining an adenosine A_3 receptor antagonist only with a chemotherapeutic agent would be sufficient to provide a beneficial therapeutic effect, in particular, an unexpected synergistic therapeutic effect.

As to the webpage by Alexis Biochemicals, it is respectfully submitted that the reference describes the general state of the art relating to multi-drug resistance, and only concurs what is already disclosed in the instant application, e.g., as disclosed on pages 4 and 5 of the instant application.

As summarized by Applicants in the previous communication, filed on February 28, 2008, the results shown in Tables 4 to 8, starting on page 23 of the instant application, clearly indicate a synergistic enhancement of the cell growth inhibitory activity of paclitaxel, docetaxel, irinotecan, vinblastine and doxorubicin in the presence of a sub-cytotoxic concentration of adenosine A_3 receptor antagonists MRE3008F20, IL-10 and IL-11 against four histologically distinct human tumor cell lines (A375 melanoma, Panc-1 pancreatic carcinoma, HT29 colon carcinoma and SKMES lung carcinoma) as determined by the measurement of the enhancement factor greater than 1. For example, as illustrated in Example 1 (starting on page 22; Table 4), MRE3008F20 (10 μg/mL), IL-10 (5 μg/mL) and IL-11 (5 μg/mL) enhanced the growth inhibitory activity of paclitaxel by 8-12 fold against the human melanoma A375 cell line at a sub-cytotoxic concentration, i.e., at a concentration well below the concentration of each individual antagonist that inhibits the

cell growth by 50% compared to the control cells (IC_{50} value) (please see Table 3 on page 21 for the IC_{50} values of the individual compounds).

The results in Table 5 (on page 24) further demonstrate that in A375 cells MRE3008F20, IL-10 and IL-11 have enhancement factors with paclitaxel and docetaxel that are indicative of a synergistic effect at each of the three sub-cytotoxic concentration tested (1, 3 and 10 μg/ml for MRE3008F20 and 0.5, 1.5 and 5 μg/ml for each of IL-10 and IL-11).

Likewise, the data in Table 6 (on page 25) demonstrate that MRE3008F20, IL-10 and IL-11 synergistically enhance the growth inhibitory activity of paclitaxel, docetaxel, irinotecan and vinblastine in human SKMES lung carcinoma cells.

Supporting data for synergistic enhancement in human HT29 colon carcinoma and Panc-1 pancreatic cancer cell lines may be found in Tables 7 and 8, respectively (on page 26).

The unexpected synergistic effects of the combinations of the present invention are further established, e.g., by colony formation experiments: MRE3008F20 (10 μM) and paclitaxel (0.75 ng/mL) each alone decreases colony formation of A375 cells to 59% and 64% of the control, respectively. Surprisingly, when MRE3008F20 is combined with paclitaxel, virtually all colony formation ceases. Since the geometrical combination predicts a result of 35%, this clearly identifies the unexpected synergistic nature of combining an adenosine A_3 receptor antagonist with a chemotherapeutic agent (please see second, third and fourth paragraphs on page 27 and Figure 2).

Additionally, a treatment of A375 cells with paclitaxel or vindesine in the absence and the presence of the adenosine A_3 receptor antagonist MRE3008F20 (10 μM) demonstrates enhancement, e.g., by reduction of the concentration exerting 50% of the G_2/M accumulation (EC_{50} value) of paclitaxel and videsine by 1.9 and 4.0 fold, respectively, in the presence of MRE3008F20 (please see last paragraph on page 28 and Figures 3A and 3C). Likewise, other adenosine A_3 receptor antagonists were shown to improve the ability of vindesine (1 nM) to alter cell proliferation in A375 cells (please see third and fourth paragraphs on page 29 and Figure 5A). The concentrations of MRE3008F20, MRE3046F20, MRE3055F20, MRE3062F20 and IL-10 that exert 50% of the enhancing activity (SEC_{50} values) in A375 cells treated with vindesine (1 nM) are

reported in Table 9 (on page 29). As can be seen the SEC_{50} values are in good agreement with inhibitory equilibrium binding constants (Ki) observed in binding experiments for the adenosine A_3 receptor.

Clearly, Applicants have evidenced that the effects of the combinations of the present invention are greater than the sum of the effects of the respective therapeutic agents separately, which is the standard applied to establish unexpected synergy.

In view of the above, reconsideration of the rejection of claims 7, 11-14 and 32-37 under 35 U.S.C. § 102(b) is respectfully requested.

Claim Rejection under 35 U.S.C. § 103(a)

Claims 7, 8, 11-16, 19 and 28-42 remain rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 6,210,917 to Carson et al. in view of U.S. Patent No. 6,066,642 to Jacobson et al. and further in view of Baraldi et al. "Pyrozolo[4,3-e]-1,2,4-triazolo[1,5-c]-pyrimidine derivatives as highly potent and selective human A_3 adenosine receptor antagonists", Journal of Medicinal Chemistry *42*, 4473-4478 (1999), and Goodman and Gilman, "The Pharmacological Basis of Therapeutics".

A. Carson et al.

In one embodiment, Carson et al. teaches a combination therapy comprising an adenosine-5'-triphosphate (ATP) depleting agent, e.g., a purine (adenine) synthesis inhibitor such as L-alanosine, to treat certain cancers that are determined to be methylthioadenosine phosphorylase (MTAse) deficient, and that are known to develop multi-drug resistance (MDR) with respect to common anti-cancer agents (please see column 4, lines 26-37 and 46-59). MTAse deficient cancers include lymphoblastic leukemias, gliomas, non-small cell lung cancers and urothelial tumors (please see column 12, lines 28-41). Quotation from Carson et al. states that in MTAse deficient cancers "Further treatment with additional anti-cancer therapies is acceptable, but not required. However, adenosine kinase inhibitors, such as those described below, can be expected to potentiate the activity of L-alanosine such that their use in conjunction with L-alanosine may be clinically desirable" (please see column 4, lines 40-45). Examples of adenosine kinase inhibitors are described in the section starting on line 9 of column 6 and ending on line 60 of column 7.

On the other hand, Carson et al. teaches that the same combination therapy may be employed to treat cancers that are determined to be MTAse competent, and that are also known to develop MDR with respect to anti-cancer agents such as vinca alkaloids, taxanes, antibiotics etc. (please see column 4, lines 46-59). MTAse competent cancers include breast cancer, colon cancer, head and neck cancer, melanoma, renal cancer, adult non-lymphoblastic leukemias and certain acute leukemias (please see column 12, lines 48-63). In accordance with Carson et al., in MTAse competent cancers "Based on the poor outcome of clinical trials and usage of purine synthesis inhibitors as anti-cancer agents in MTAse competent cells, it is unlikely that the inhibitors will exert a significant anti-cancer effect on such cells. Rather, in this embodiment of the invention, the anti-cancer therapy is provided by other therapeutic agents" (please see column 4, lines 61-67).

Accordingly, Carson et al. suggests that by combining an adenosine kinase inhibitor with a purine synthesis inhibitor such as L-alanosine for the treatment of MTAse deficient cancers may potentiate the activity of the purine synthesis inhibitor, whereas no such effect is expected when the purine synthesis inhibitor is employed to treat MTAse competent cancers in combination with therapeutic drugs such as vinca alkaloids, taxanes, antibiotics etc.

B. *Jacobson et al.*

Jacobson et al. teaches the use of adenosine A_3 receptor antagonists in the killing of cancer cells (Example 31, column 63), wherein the A_3 receptor antagonists may be used alone, or in combination with other pharmaceutically active compounds.

C. *Fishman et al.*

Fishman et al. have demonstrated that the inhibitory effect of adenosine on lymphoma cell growth is abolished in the presence of the adenosine A_3 receptor antagonist MRS-1220 (second full paragraph and Fig. 4 on page 1455), whereas the adenosine A_3 receptor agonist IB-MECA mimicked the inhibitory effect of adenosine (third full paragraph and Fig. 5 on page 1455).

D. *Baraldi et al.*

Baraldi et al. teaches that MRE3008F20 is an adenosine A_3 receptor antagonist.

E. Goodman and Gilman

Goodman and Gilman describes the general state of art in the chemotherapeutic treatment of neoplastic diseases. For example, it is noted that local means of therapy, such as surgery and irradiation, is routinely followed by adjuvant chemotherapy (page 1225). Goodman and Gilman further teaches that drugs are generally more effective in combination and may be synergistic through biochemical interactions (page 1230).

Clearly, there is nothing in Carson et al. that does teach or suggest, whether taken alone or when combined with other references, that adenosine A_3 receptor antagonists MRE3008F20, MRE3046F20, MRE3055F20, MRE3062F20, IL-10 and IL-11 can synergistically enhance the chemotherapeutic treatment of melanoma, pancreatic carcinoma, colon carcinoma and lung carcinoma when combined with paclitaxel, docetaxel, irinotecan, videsine, vinblastine or doxorubicin, as disclosed and claimed by the instant invention.

As to the Examiner's opinion that only a specific concentration of the adenosine A_3 receptor antagonists is shown to be synergistic with a specific concentration of specific chemotherapeutic cancer agents, it is respectfully submitted that Applicants have demonstrated synergy by employing a cell growth inhibitory assay to determine the IC_{50} values of the chemotherapeutic agents in the absence and the presence of selected sub-cytotoxic concentrations of adenosine A_3 receptor antagonists. A synergistic therapeutic effect is achieved when the IC_{50} value of the chemotherapeutic agent is lower in the presence of the adenosine A_3 receptor, i.e., the enhancement factor is greater than 1. The IC_{50} values are determined by using various properly selected concentrations of the chemotherapeutic agent (please see pages 17 and 18). Moreover, the enhancement factors for paclitaxel and docetaxel in A375 cells were determined in the presence of three different sub-cytotoxic concentrations of MRE3008F20, IL-10 and IL-11. As the data in Table 5 (page 24) indicate, in each case an enhancement is achieved even at the lowest concentration. Based upon these data, the enhancement factors in the other human tumor cell lines were determined in the presence of the lowest dose of the adenosine A_3 receptor antagonists.

Furthermore, Applicants have determined the SEC_{50} values for the adenosine A_3 receptor antagonists MRE3008F20, MRE3046F20, MRE3055F20, MRE3062F20 and IL-10 in A375 cells treated with 1 nM vindesine (Table 9, page 29).

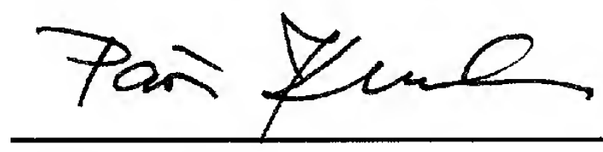
In view of the foregoing and all the claim limitations set forth in claim 7, it is respectfully submitted that all the instant claims 7, 11-14 and 32-37 are fully supported by the enabling disclosure of the instant application.

Reconsideration of the rejection of claims 7, 11-14 and 32-37 under 35 U.S.C. § 103(a) is respectfully requested.

Conclusion

The instant application is now believed to be in condition for allowance and such is earnestly solicited.

Respectfully submitted,



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